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Tomoko ASAKAWA

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For: AGENT FOR TREATING DIABETES

**VERIFICATION OF ENGLISH TRANSLATION**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

I, Michiko MATSUTANI, declare that I am conversant in both the Japanese and English languages and that the English translation as attached hereto is an accurate translation of Japanese Patent Application No. 2003-345740 filed on October 3, 2003.

Signed this 11th day of August, 2010.



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Michiko MATSUTANI

JAPAN PATENT OFFICE

This is to certify that the annexed is a true copy of the following application as filed with this Office.

Date of Application: October 3, 2003

Application Number: Patent Application No. 2003-345740

The country code and number  
of your priority application,  
to be used for filing abroad  
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Applicant(s): TAKEDA PHARMACEUTICAL COMPANY LIMITED  
(TAKEDA CHEMICAL INDUSTRIES, LTD.)

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Registration Nos.  
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0203423

Document Name: Claims

1. An agent for treating diabetes with sulfonylurea secondary failure which comprises a dipeptidyl peptidase IV inhibitor.

5        2. The agent according to claim 1, wherein the sulfonylurea secondary failure is caused by a sulfonylurea compound.

10       3. The agent according to claim 1, wherein the sulfonylurea secondary failure is caused by a fast-acting insulin secretagogue.

Document Name: Specification

Title of the Invention:

AGENT FOR TREATING DIABETES

Technical Field

5 [0001]

The present invention relates to an agent for treating diabetes with sulfonylurea secondary failure which comprises a dipeptidyl peptidase IV (hereinafter sometimes referred to as DPP-IV) inhibitor.

10 Background Art

[0002]

A sulfonylurea compound (hereinafter sometimes referred to as an SU agent) has been generally used as a first-choice oral hypoglycemic agent. Repeated  
15 administration of an SU agent to a diabetic patient, however, may cause the patient a condition in which the agent is ineffective in lowering the blood sugar level, namely sulfonylurea secondary failure.

Diabetic patients with sulfonylurea secondary failure  
20 are treated with insulin preparations because administration of SU agents is not expected to make therapeutic effect on them.

DPP-IV inhibitors are known to be useful as agents for treating diabetes (see, for example, Patent Document 1).

25 [0003]

## Patent Document 1: International Publication

No.WO02/062764 Pamphlet

## Disclosure of the Invention

## Problems to be solved by the Invention

5 [0004]

An object of the present invention is to provide an agent for treating diabetes with sulfonylurea secondary failure showing excellent insulin-secreting and hypoglycemic effects on even diabetic patients on whom a  
10 sulfonylurea compound or a fast-acting insulin secretagogue has no insulin-secreting effect and therefore no sufficient hypoglycemic effect.

[0005]

Another object of the present invention is to provide  
15 an agent for treating diabetes with sulfonylurea secondary failure having no side effect such as vascular complications and hypoglycemia which are caused by administration (especially long-term administration) of an insulin preparation to diabetic patients with sulfonylurea  
20 secondary failure and showing excellent therapeutic effect.

## Means for Solving the Problem

[0006]

As a result of intensive study, the present inventors found for the first time that a DPP-IV inhibitor was useful  
25 as an agent for treating diabetes with sulfonylurea

secondary failure, and then completed the present invention.

That is, the present invention relates to:

1) An agent for treating diabetes with sulfonylurea  
secondary failure which comprises a dipeptidyl peptidase IV  
inhibitor;

2) The agent according to the above 1), wherein the  
sulfonylurea secondary failure is caused by a sulfonylurea  
compound;

3) The agent according to the above 1), wherein the  
sulfonylurea secondary failure is caused by a fast-acting  
insulin secretagogue; and the like.

#### Effect of the Invention

[0007]

The agent for treating diabetes with sulfonylurea  
secondary failure of the present invention shows excellent  
insulin-secreting and hypoglycemic effects on even diabetic  
patients on whom a sulfonylurea compound or a fast-acting  
insulin secretagogue has no insulin-secreting effect and  
therefore no sufficient hypoglycemic effect.

#### Best Mode for Carrying Out the Invention

[0008]

In the specification, a DPP-IV inhibitor means a  
compound that inhibits the enzyme activity of DPP-IV  
[EC3.4.14.5 according to classification by the Committee  
for Nomenclature, International Union of Biochemistry and

Molecular Biology (IUBMB)]. The compound may be peptidic or nonpeptidic, and it is preferably nonpeptidic.

The form of a DPP-IV inhibitor may be different between before and after administration into the body as long as the DPP-IV inhibiting activity is retained. That is, a DPP-IV inhibitor may be an "active metabolite" having the DPP-IV inhibiting activity after the DPP-IV inhibitor is metabolized in vivo to a substance with a different structure. In addition, a DPP-IV inhibitor may be a "prodrug" that is changed into an active substance as a result of reaction with an enzyme, gastric acid, etc. under the physiological conditions in vivo.

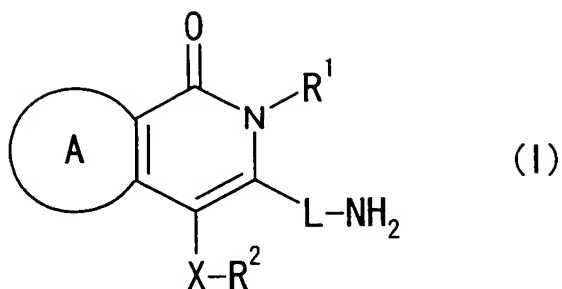
The DPP-IV inhibiting activity can be confirmed with a method utilizing "the method of Raymond et al. (Diabetes, Vol.47, pp.1253-1258, 1998)".

[0009]

DPP-IV inhibitors include nitrogen-containing heterocyclic compounds, specifically, the following compounds (1) to (8).

(1) A compound of the formula:  
[Chemical formula 1]





wherein, the ring A is an optionally substituted 5 to 10-membered aromatic ring,

R<sup>1</sup> and R<sup>2</sup> are the same or different and are independently an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group,

X is a bond, -O-, -S-, -SO-, -SO<sub>2</sub>- or -NR<sup>3</sup>- (wherein R<sup>3</sup> is a hydrogen atom or an optionally substituted hydrocarbon group), and

L is a divalent hydrocarbon group, or a salt thereof, as disclosed in WO02/062764.

[0010]

A salt of the compound of the formula (I) is preferably a pharmacologically acceptable salt. Such a salt includes, for example, salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids, and salts with basic or acidic amino acids.

Preferred examples of salts with inorganic bases include salts with alkali metals such as sodium and potassium; alkaline earth metals such as calcium and

magnesium; aluminum, ammonium and the like.

Preferred examples of salts with organic bases include salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N-dibenzylethylenediamine and the like.

Preferred examples of salts with inorganic acids include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like.

Preferred examples of salts with organic acids include salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like.

Preferred examples of salts with basic amino acids include salts with arginine, lysine, ornithine and the like.

Preferred examples of salts with acidic amino acids include salts with aspartic acid, glutamic acid and the like.

The compound of the formula (I) may be anhydrous or hydrous, and further may be a prodrug.

[0011]

Preferred examples of the compound of the formula (I) include the following compounds.

(Compound I-a)

A compound wherein the ring A is a benzene ring optionally substituted with 1 or 2 substituents selected from

1) cyano;

- 5 2) C<sub>1-10</sub> alkyl (preferably ethyl) or C<sub>2-10</sub> alkenyl (preferably ethenyl), each of which may be optionally substituted with carbamoyl or carboxyl;
- 3) optionally substituted hydroxyl [preferably, C<sub>1-10</sub> alkoxy (preferably methoxy, isopropoxy) optionally substituted with 1 to 3 substituents selected from carbamoyl, carboxyl and C<sub>2-5</sub> alkoxycarbonyl (preferably methoxycarbonyl); hydroxyl; C<sub>7-13</sub> aralkyloxy (preferably benzyloxy)] [more preferably, carbamoylmethoxy];
- 10 4) acyl [preferably, C<sub>1-6</sub> alkyl-carbonyl (preferably acetyl), carbamoyl, mono- or di-(C<sub>1-6</sub> alkyl optionally substituted with 1 to 3 substituents selected from halogen and C<sub>1-6</sub> alkoxy-carbonyl)-carbamoyl (preferably methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, dimethylcarbamoyl, trifluoroethylcarbamoyl, ethoxycarbonylmethylcarbamoyl and
- 15 the like), C<sub>3-10</sub> cycloalkyl-carbamoyl (preferably cyclopropylcarbamoyl), C<sub>7-13</sub> aralkyl-carbamoyl (preferably benzylcarbamoyl), nitrogen-containing heterocyclic-carbonyl optionally substituted with hydroxy (preferably pyrrolidinylcarbonyl, piperidinocarbonyl), C<sub>1-6</sub>
- 20 alkylsulfonyl (preferably methylsulfonyl), C<sub>1-6</sub>

alkylsulfinyl (preferably methylsulfinyl), carboxyl, C<sub>1-6</sub>  
alkoxy-carbonyl (preferably methoxycarbonyl),  
thiocarbamoyl];

5) optionally substituted amino (preferably  
5 carbamoylamino);

6) optionally substituted thiol [preferably C<sub>1-10</sub> alkylthio  
(preferably methylthio) optionally substituted with  
carbamoyl];

7) optionally substituted heterocyclic group [preferably,  
10 an aromatic heterocyclic group (preferably, furyl, thienyl,  
oxazolyl, oxadiazolyl, thiazolyl, tetrazolyl, pyridyl,  
pyrrolyl, triazolyl) or a nonaromatic heterocyclic group  
(preferably, dioxoisindol, 5-oxooxadiazol-3-yl, 5-  
oxothiadiazol-3-yl), each of which may be optionally  
15 substituted with 1 or 2 substituents selected from C<sub>1-6</sub>  
alkyl optionally substituted with 1 to 3 halogen atoms  
(preferably methyl, trifluoromethyl), carboxyl, C<sub>2-8</sub>  
alkoxycarbonyl (preferably ethoxycarbonyl), cyano,  
carbamoyl, amino, mono- or di-C<sub>2-10</sub> alkanoylamino (e.g.  
20 acetylamino, isopentanoylamino), C<sub>1-10</sub> alkoxy-carbonylamino  
(e.g. methoxycarbonylamino), carbamoylamino, mono- or di-  
C<sub>1-10</sub> alkyl-carbamoylamino (e.g. methylcarbamoylamino,  
dimethylcarbamoylamino), C<sub>6-14</sub> aryl-carbonylamino (e.g.  
benzoylamino), C<sub>3-10</sub> cycloalkyl-carbonylamino, C<sub>7-13</sub>  
25 aralkyloxy-carbonylamino, mono- or di-C<sub>1-10</sub>

alkylsulfonylamino (e.g. methylsulfonylamino, dimethylsulfonylamino), C<sub>6-14</sub> arylsulfonylamino and C<sub>1-6</sub> alkoxy-carbamoylamino (e.g. methoxycarbamoylamino)]; and  
8) amidino;

5           R<sup>1</sup> is C<sub>4-10</sub> alkyl (preferably isobutyl, neopentyl) or C<sub>4-10</sub> cycloalkylalkyl (preferably cyclopropylmethyl);

          R<sup>2</sup> is a C<sub>6-14</sub> aryl (preferably phenyl) optionally substituted with 1 or 2 substituents selected from halogen (preferably fluorine, chlorine) and C<sub>1-6</sub> alkyl (preferably  
10 methyl);

          X is a bond; and

          L is C<sub>1-10</sub> alkylene (preferably -CH<sub>2</sub>-).

[0012]

(Compound I-b)

15           A compound wherein the ring A is a benzene ring optionally substituted with 1 or 2 substituents selected from

- 1) C<sub>1-10</sub> alkyl (preferably ethyl) or C<sub>2-10</sub> alkenyl (preferably ethenyl), each of which may be optionally  
20 substituted with C<sub>2-8</sub> alkoxy carbonyl (preferably ethoxy carbonyl) or carbamoyl;  
2) optionally substituted hydroxyl [preferably, C<sub>1-10</sub> alkoxy (preferably methoxy) optionally substituted with carbamoyl; more preferably carbamoylmethoxy];  
25 3) acyl (preferably carbamoyl, thiocarbamoyl, carboxyl);

and

4) optionally substituted heterocyclic group [preferably, an aromatic heterocyclic group (preferably, furyl, thienyl, oxazolyl, oxadiazolyl, thiazolyl, tetrazolyl, pyridyl, pyrrolyl, triazolyl) or a nonaromatic heterocyclic group (preferably, 5-oxooxadiazol-3-yl), each of which may be optionally substituted with 1 or 2 substituents selected from C<sub>1-6</sub> alkyl (preferably methyl), carboxyl, C<sub>2-8</sub> alkoxy-carbonyl (preferably ethoxy-carbonyl), cyano, carbamoyl, amino, mono- or di-C<sub>2-10</sub> alkanoylamino (e.g. acetylamino, isopentanoylamino), C<sub>1-10</sub> alkoxy-carbonylamino (e.g. methoxy-carbonylamino), carbamoylamino, mono- or di-C<sub>1-10</sub> alkyl-carbamoylamino (e.g. methylcarbamoylamino, dimethylcarbamoylamino), C<sub>6-14</sub> aryl-carbonylamino (e.g. benzoylamino), C<sub>3-10</sub> cycloalkyl-carbonylamino, C<sub>7-13</sub> aralkyloxy-carbonylamino, mono- or di-C<sub>1-10</sub> alkylsulfonylamino (e.g. methylsulfonylamino, dimethylsulfonylamino), C<sub>6-14</sub> arylsulfonylamino and C<sub>1-6</sub> alkoxy-carbamoylamino (e.g. methoxy-carbamoylamino)];

20        R<sup>1</sup> is C<sub>4-10</sub> alkyl (preferably isobutyl, neopentyl) or C<sub>4-10</sub> cycloalkylalkyl (preferably cyclopropylmethyl);

      R<sup>2</sup> is C<sub>1-10</sub> alkyl (preferably butyl) optionally substituted with 1 to 3 halogen atoms;

      X is -O-; and

25        L is C<sub>1-10</sub> alkylene (preferably -CH<sub>2</sub>-).

[0013]

Among the compounds of the formula (I), particularly preferred are 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazol-4-carbonitrile;

5 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazol-4-carboxylic acid;

2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazol-4-carboxamide;

10 ethyl 2-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-1,3-thiazol-4-carboxylate;

(E)-3-[3-(aminomethyl)-4-butoxy-2-isobutyl-1-oxo-1,2-dihydro-6-isoquinolyl]-2-propenamide;

(E)-3-[3-(aminomethyl)-2-isobutyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]-2-propenamide;

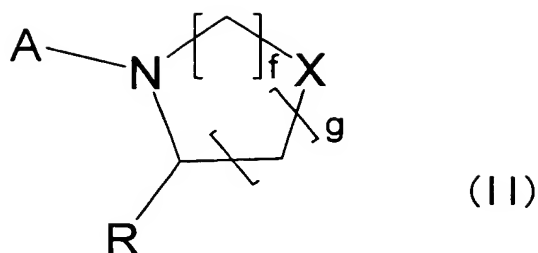
15 3-(aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarboxamide;

2-([3-(aminomethyl)-2-isobutyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]oxy)acetamide, and the like.

[0014]

20 (2) A compound of the formula:

[Chemical formula 2]



wherein, f is 1 or 2; g is 0, 1 or 2; X is -CH<sub>2</sub>-, -O-, -S-,  
 -SO-, -SO<sub>2</sub>- or -NR<sup>3</sup>- (wherein R<sup>3</sup> is hydrogen or C<sub>1-6</sub> alkyl);  
 R is hydrogen, cyano, -CHO, -B(OH)<sub>2</sub>-, -P(O)(OR<sup>3</sup>), -CCR<sup>4</sup> or -  
 5 CH=NR<sup>5</sup> (wherein R<sup>4</sup> is hydrogen, fluorine, C<sub>1-6</sub> alkyl, cyano,  
 nitro, -OR<sup>3</sup>, -CO<sub>2</sub>R<sup>3</sup> or -COR<sup>3</sup> (wherein R<sup>3</sup> is as defined  
 above); R<sup>5</sup> is phenyl, hydroxyl, -OR<sup>3</sup>, -OCOR<sup>3</sup> or benzyloxy  
 (wherein R<sup>3</sup> is as defined above)); and A is an optionally  
 substituted amino acid residue, or a salt thereof, as  
 10 disclosed in WO95/15309 etc.

In the formula, the C<sub>1-6</sub> alkyl represented by R<sup>3</sup>  
 includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl,  
 sec-butyl, t-butyl, pentyl, isopentyl, neopentyl, 1-  
 ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-  
 15 dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, and the  
 like.

[0015]

The amino acid residue of the "optionally substituted  
 amino acid residue" represented by A includes a group after  
 20 removing the OH of the constitutive carboxyl group from α-  
 amino acid or β-amino acid.



The  $\alpha$ -amino acid includes alanine, arginine, asparagine, aspartic acid, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, citrulline, ornithine, homocysteine, and the like.

The  $\beta$ -amino acid includes  $\beta$ -alanine,  $\beta$ -aminocyclopropanoic acid,  $\beta$ -aminocyclobutanoic acid,  $\beta$ -aminocyclopentanoic acid,  $\beta$ -aminocyclohexanoic acid,  $\beta$ -aminocycloheptanoic acid,  $\beta$ -aminocyclooctanoic acid, and the like. The  $\beta$ -amino acid may have an unsaturated bond in the carbon chain constituting the amino acid.

The above-mentioned  $\alpha$ -amino acid and  $\beta$ -amino acid may be of D-, L- or DL-form, and preferably of natural L-form.

[0016]

The above-mentioned amino acid residue may be optionally substituted with 1 or 2 substituents on an amino group constituting the amino acid or on the side chain of the amino acid.

The above-mentioned "substituent on the amino group" is preferably an optionally substituted hydrocarbon group, an optionally substituted piperidinyl group, or the like.

The hydrocarbon group of the "optionally substituted hydrocarbon group" includes  $C_{1-6}$  alkyl,  $C_{3-12}$  cycloalkyl,  $C_{2-6}$  alkenyl,  $C_{3-12}$  cycloalkenyl,  $C_{2-6}$  alkynyl,  $C_{4-12}$

cycloalkadienyl, C<sub>6-14</sub> aryl (preferably phenyl), C<sub>7-15</sub> aralkyl (preferably benzyl, phenethyl), adamantyl, bicyclo[2.2.1]heptyl, and bicyclo[3.1.1]heptyl.

5 The hydrocarbon group may be optionally substituted with 1 to 3 substituents at substitutable positions, and such substituents include halogen (preferably fluorine, chlorine); cyano; hydroxyl optionally substituted with acyl; hydroxymethyl; C<sub>1-6</sub> alkoxy optionally substituted with 1 to 3 halogen atoms (preferably fluorine); and amino  
10 optionally mono- or di-substituted with optionally substituted C<sub>6-14</sub> aryl or an optionally substituted heterocyclic group.

The acyl of "hydroxyl optionally substituted with acyl" includes the acyl exemplified above as substituents  
15 of the ring A in Compound I-a.

The C<sub>6-14</sub> aryl of the "optionally substituted C<sub>6-14</sub> aryl" includes phenyl, naphthyl, and the like.

The heterocyclic group of the "optionally substituted heterocyclic group" includes pyridyl, pyrimidyl, pirazyl, quinolyl, isoquinolyl, quinoxalyl, and the like.  
20

The C<sub>6-14</sub> aryl and the heterocyclic group may be optionally substituted with 1 to 3 substituents at substitutable positions, and such substituents include halogen (preferably fluorine, chlorine, bromine); cyano; nitro; C<sub>1-6</sub> alkyl; C<sub>1-6</sub> alkoxy optionally substituted with 1  
25

to 3 halogen atoms (preferably fluorine); carboxyl; carbamoyl; C<sub>1-6</sub> alkylsulfonyl (preferably methanesulfonyl); aminosulfonyl optionally mono- or di-substituted with C<sub>1-6</sub> alkyl (preferably dimethylaminosulfonyl); and the like.

5       The substituent for the above-mentioned "optionally substituted hydrocarbon group" is especially preferably 5-nitro-2-pyridylamino, 5-cyano-2-pyridylamino, 2-pyrimidylamino, 2-pyrazylamino, or the like.

10       The substituent for the above-mentioned "optionally substituted piperidinyll" includes C<sub>1-6</sub> alkyl; hydroxymethyl; and the "optionally substituted C<sub>6-14</sub> aryl" and the "optionally substituted heterocyclic group" exemplified above for the above-mentioned "amino optionally mono- or di-substituted with optionally substituted C<sub>6-14</sub> aryl or an  
15       optionally substituted heterocyclic group". The number of substituents is, for example, 1 to 3.

[0017]

20       The above-mentioned "substituent on the side chain of the amino acid" includes an optionally substituted hydrocarbon group, hydroxyl, C<sub>1-10</sub> alkoxy optionally substituted with 1 to 3 halogen atoms (preferably fluorine), acyl, optionally substituted amino, and the like.

25       The hydrocarbon of the "optionally substituted hydrocarbon group" includes C<sub>1-10</sub> alkyl, C<sub>3-12</sub> cycloalkyl, C<sub>2-10</sub> alkenyl, C<sub>3-12</sub> cycloalkenyl, and the like.

The hydrocarbon may be optionally substituted with 1 to 3 substituents at substitutable positions, and such substituents include amino, C<sub>1-6</sub> alkyl-carbonylamino (preferably acetylamino), hydroxy, C<sub>1-6</sub> alkoxy, heterocyclic groups (preferably pyridyl), and the like.

The above-mentioned "acyl" is preferably optionally substituted nitrogen-containing heterocyclic-carbonyl. The "optionally substituted nitrogen-containing heterocycle" includes a nitrogen-containing heterocycle (preferably pyridine, pyridazine, pyrimidine, pyrazine, imidazole, pyrazole, thiazole, isothiazole, oxazole, isoxazole, or the like) optionally substituted with 1 to 3 substituents selected from halogen (preferably fluorine, chlorine, bromine), cyano, nitro, C<sub>1-6</sub> alkyl optionally substituted with 1 to 3 halogen atoms (preferably fluorine) (e.g. trifluoromethyl), C<sub>1-6</sub> alkoxy, amino optionally mono- or di-substituted with C<sub>1-6</sub> alkyl, hydroxy, carboxyl and C<sub>1-6</sub> alkyl-oxycarbonyl, and the like.

The substituent for the above-mentioned "optionally substituted amino" includes C<sub>1-6</sub> alkyl optionally substituted with 1 to 3 substituents selected from carboxyl, carbamoyl, C<sub>1-6</sub> alkyl-oxycarbonyl and a nitrogen-containing heterocyclic group (preferably pyridyl), and the like. Such a substituent may optionally bind to hydroxyl, carboxyl, amino, or the like on the side chain of the amino

acid.

[0018]

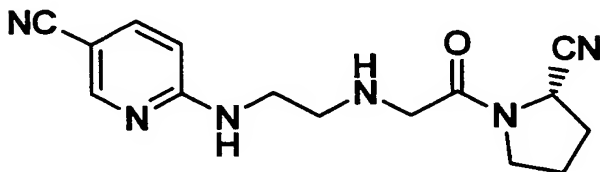
The salt of the compound of the formula (II) includes salts similar to a salt of the compound of the formula (I).

5 The compound of the formula (II) may be anhydrous or hydrous, and further may be a prodrug.

[0019]

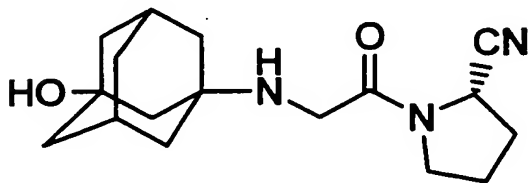
Preferred examples of the compound of the formula (II) include N-(N'-substituted glycyl)-2-cyano-pyrrolidine derivatives such as (2S)-1-{{{2-[(5-cyanopyridin-2-yl)amino]ethyl}amino}acetyl}-2-cyano-pyrrolidine (DPP-728) (as disclosed in WO98/19998) of the formula:

[Chemical formula 3]



15 (2S)-1-[[[(3-hydroxy-1-adamantyl)amino]acetyl]-2-cyano-pyrrolidine (LAF238) (as disclosed in WO00/34241) of the formula:

[Chemical formula 4]

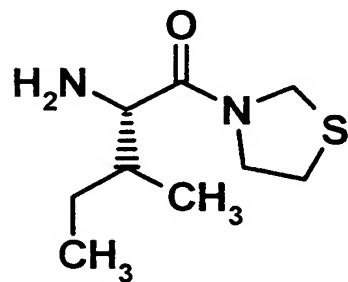


(2S)-1-{{{2-[(1-pyrimidin-2-yl)piperidin-4-yl]amino}acetyl}-  
2-cyano-pyrrolidine (as disclosed in WO02/30890),

(2S)-1-{{{2-[(pyrazin-2-yl)amino]ethyl}amino}acetyl}-2-  
cyano-pyrrolidine, and (S)-1-[1-[5-(N,N-

5 dimethylaminosulfonyl)-2-pyridylamino]-2-methyl-2-  
propylamino}acetyl-2-pyrrolidinecarbonitrile (K-361) (as  
disclosed in WO02/51836);

thiazolidine or pyrrolidine derivatives such as L-threo-  
isoleucyl thiazolidine (P32/98) of the formula:



L-allo-isoleucyl thiazolidine, L-threo-isoleucyl  
pyrrolidine, L-allo-isoleucyl pyrrolidine and L-valyl  
pyrrolidine (as disclosed in WO01/72290 etc.); and the like.

15 [0020]

(3) N-substituted 2-cyanopyrrole and 2-cyanopyrroline  
derivatives as disclosed in WO01/55105, preferably, (S,S)-  
1-(2-amino-3,3-dimethylbutyryl)-2,5-dihydro-1H-pyrrol-2-  
carbonitrile.

20 (4) Heterocyclic compounds as disclosed in WO02/02560,  
preferably, 7-benzyl-8-[6-(hydroxymethyl)-1,4-diazepan-1-

yl]-1,3-dimethyl-3,7-dihydropurine-2,6-dione.

(5) Pyrrolidine derivatives fused to cyclopropane as disclosed in WO01/68603, preferably, (1S,3S,5S)-2-[(2S)-2-amino-3,3-dimethylbutyryl]-3-cyano-2-

5 azabicyclo[3.1.0]hexane.

(6) Proline derivatives as disclosed in WO02/14271, preferably, (2S)-1-[(2S,4S)-4-(3-chloro-4-cyanophenyl)amino-2-pyrrolidinylcarbonyl]-2-cyanopyrrolidine.

10 (7) Cyanopyrrolidine derivatives as disclosed in WO02/38541, preferably, (2S,4S)-1-[(2S,3S)-2-amino-3-methyl-pentanoyl]-2-cyano-4-fluoropyrrolidine, (2S,4S)-2-cyano-4-fluoro-1-[(1-hydroxymethyl)cyclopentylamino]acetylpyrrolidine, and (2S,4S)-2-cyano-4-fluoro-1-(1-hydroxy-3-

15 adamantylamino)acetylpyrrolidine.

(8) Compounds as disclosed in WO02/02560, WO 03/055881, WO 03/040174, WO 03/037327, WO 03/035057, WO 03/035067, WO 03/024942, WO 03/024965, WO 03/004498, WO 03/004496, WO 03/000250, WO 03/002530, WO 03/002531, WO 03/002553, WO

20 03/000180, WO 03/000181, EP 1258476, WO 0251836, WO 02/68420, US 6432969, etc.; P93/01 and the like.

[0021]

As the agent for treating diabetes with sulfonylurea secondary failure of the present invention (hereinafter,

25 sometimes abbreviated to the agent of the present

invention), a DPP-IV inhibitor as it is or as a pharmaceutical composition prepared by mixing with a pharmacologically acceptable carrier and the like can be administered to a mammal (e.g. human, mouse, rat, rabbit,  
5 dog, cat, cow, horse, pig, monkey).

The amount of a DPP-IV inhibitor contained in the agent of the present invention varies on the type of the DPP-IV inhibitor, the size of the agent, and the like. For example, it is 1 to 90% by weight, preferably 5 to 80 % by  
10 weight.

The above-mentioned pharmacologically acceptable carrier includes various organic or inorganic carriers that are conventionally used as materials for drug formulation. The carrier is incorporated into a solid preparation as an  
15 excipient, a lubricant, a binder, a disintegrant or the like; or into a liquid preparation as a solvent, a solubilizing agent, a suspending agent, an isotonicity, a buffering agent, a soothing agent or the like. Additives for drug formulation such as an antiseptic, an antioxidant,  
20 a colorant, a sweetening agent and the like may be also used, if necessary.

Preferred examples of the excipient include lactose, saccharose, D-mannitol, D-sorbitol, starch, pregelatinized starch, dextrin, crystalline cellulose, low-substituted  
25 hydroxypropylcellulose, carboxymethylcellulose sodium,



acacia, pullulan, light anhydrous silicic acid, synthetic aluminum silicate, magnesium aluminometasilicate, and the like.

Preferred examples of the lubricant include magnesium  
5 stearate, calcium stearate, talc, colloidal silica, and the like.

Preferred examples of the binder include  
pregelatinized starch, sucrose, gelatin, acacia,  
methylcellulose, carboxymethylcellulose,  
10 carboxymethylcellulose sodium, crystalline cellulose,  
saccharose, D-mannitol, trehalose, dextrin, pullulan,  
hydroxypropylcellulose, hydroxypropylmethylcellulose,  
polyvinylpyrrolidone, and the like.

Preferred examples of the disintegrant include lactose,  
15 saccharose, starch, carboxymethylcellulose,  
carboxymethylcellulose calcium, croscarmellose sodium,  
carboxymethylstarch sodium, light anhydrous silicic acid,  
low-substituted hydroxypropylcellulose, and the like.

[0022]

20 Preferred examples of a solvent include water for  
injection, physiological saline, Ringer's solution, alcohol,  
propylene glycol, polyethylene glycol, sesame oil, corn oil,  
olive oil, cotton seed oil, and the like.

Preferred examples of the solubilizing agent include  
25 polyethylene glycol, propylene glycol, D-mannitol,

trehalose, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, sodium salicylate, sodium acetate, and the like.

Preferred examples of the suspending agent include  
5 surfactants such as stearyl triethanolamine, sodium laurylsulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride and glyceryl monostearate; hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose  
10 sodium, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose and hydroxypropylcellulose; polysorbates, polyoxyethylene hydrogenated castor oil, and the like.

[0023]

15 Preferred examples of the isotonicity include sodium chloride, glycerin, D-mannitol, D-sorbitol, glucose, and the like.

Preferred examples of the buffering agent include buffers of phosphate, acetate, carbonate and citrate, and  
20 the like.

Preferred examples of the soothing agent include benzyl alcohol, and the like.

Preferred examples of the antiseptic include p-hydroxybenzoic acid esters, chlorobutanol, benzyl alcohol,  
25 phenethyl alcohol, dehydroacetic acid, sorbic acid, and the

like.

Preferred examples of the antioxidant include sulfite, ascorbate, and the like.

Preferred examples of the colorant include water-soluble food tar dyes (e.g. food dyes such as food red No.2 and No.3, food yellow No.4 and No.5, and food blue No.1 and No.2), water-insoluble lake dyes (e.g. aluminum salts of the above-mentioned water-soluble food tar dyes), natural dyes (e.g.  $\beta$ -carotene, chlorophyll, red ocher, yellow iron sesquioxide), and the like.

Preferred examples of the sweetening agent include saccharin sodium, dipotassium glycyrrhizinate, aspartame, stevia, and the like.

[0024]

The dosage forms of the agent of the present invention include oral preparations such as tablets (including sublingual tablets and intraorally disintegrating tablets), capsules (including soft capsules and microcapsules), granules, powders, troches, syrups, emulsions and suspensions; and parenteral preparations such as injections (e.g. subcutaneous injections, intravenous injections, intramuscular injections, intraperitoneal injections), external preparations (e.g. nasal preparations, percutaneous preparations, ointments and the like), suppositories (e.g. rectal suppositories and vaginal

suppositories), pellets, preparations for drip infusion, eye drops, and preparations for transpulmonary administration (inhalants and the like). These preparations can be orally or parenterally safely administered. These preparations may be controlled-release preparations such as immediate-release preparations or sustained-release preparations (for example, sustained-release microcapsules).

The agent of the present invention can be manufactured with a conventional method in the art, for example, a method described in the Japanese Pharmacopoeia or the like. Hereinafter, specific methods for manufacture of the preparations are explained in detail.

[0025]

An oral preparation, for example, is manufactured by adding an excipient (e.g. lactose, saccharose, starch, D-mannitol or the like), a disintegrant (e.g. carboxymethylcellulose calcium or the like), a binder (e.g. pregelatinized starch, acacia, carboxymethylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone or the like) or a lubricant (e.g. talc, magnesium stearate, polyethylene glycol 6000 or the like) to the active ingredient, compression molding the mixture, and then, if necessary, coating the resulting molded product with a coating base according to a method per se known for the purpose of

masking of taste or making the preparation enteric or sustained-release.

The coating base includes a sugar coating base, a water-soluble film coating base, an enteric film coating base, a sustained-release film coating base, and the like.

As the sugar coating base, saccharose may be used or may be used in combination with 1 or 2 selected from talc, precipitated calcium carbonate, gelatin, acacia, pullulan, carnauba wax and the like.

The water-soluble film coating base includes cellulose polymers such as hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose and methylhydroxyethylcellulose; synthetic polymers such as polyvinylacetal diethylaminoacetate, aminoalkylmethacrylate copolymer E [Eudragit E (trade name), Roehm Pharma] and polyvinylpyrrolidone; polysaccharides such as pullulan; and the like.

[0026]

The enteric film coating base includes cellulose polymers such as hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, carboxymethylethylcellulose, and cellulose acetate phthalate; acrylate polymers such as methacrylate copolymer L [Eudragit L (trade name), Roehm Pharma], methacrylate copolymer LD [Eudragit L-30D55 (trade name), Roehm Pharma],

and methacrylate copolymer S [Eudragit S (trade name),  
Roehm Pharma]; natural products such as shellac; and the  
like.

The sustained-release film coating base includes  
5 cellulose polymers such as ethyl cellulose; acrylate  
polymers such as aminoalkylmethacrylate copolymer RS  
[Eudragit RS (trade name), Roehm Pharma] and ethyl  
acrylate/methyl methacrylate copolymer suspension [Eudragit  
NE (trade name), Roehm Pharma]; and the like.

10 Two or more of the above-mentioned coating bases may  
be mixed at an appropriate proportion and then used. In a  
coating step, a light-blocking agent such as titanium  
dioxide or iron sesquioxide may be also used.

[0027]

15 An injection is manufactured by dissolving, suspending  
or emulsifying the active ingredient in a water-soluble  
solvent (e.g. distilled water, physiological saline,  
Ringer's solution, or the like) or an oily solvent (e.g. a  
vegetable oil such as olive oil, sesame oil, cotton seed  
20 oil or corn oil, propylene glycol, or the like) together  
with a dispersing agent (e.g. Polysorbate 80,  
polyoxyethylene hydrogenated caster oil 60, polyethylene  
glycol, carboxymethylcellulose, sodium arginate, or the  
like), a preservative (e.g. methylparaben, propylparaben,  
25 benzyl alcohol, chlorobutanol, phenol, or the like), an

isotonicity (e.g. sodium chloride, glycerin, D-mannitol, D-sorbitol, glucose, or the like) and the like. In this process, additives such as a solubilizing agent (e.g. sodium salicylate, sodium acetate, or the like), a  
5 stabilizer (e.g. human serum albumin, or the like), a soothing agent (e.g. benzyl alcohol, or the like) and the like may be used, if necessary.

Among the above-mentioned various preparations, preferred are oral preparations which are excellent in  
10 convenience in use or compliance.

[0028]

In the specification, the "sulfonylurea secondary failure" of "diabetes with sulfonylurea secondary failure" means a condition in which "a drug that promotes insulin  
15 secretion from pancreatic  $\beta$ -cells by binding to the sulfonylurea receptor 1 (SUR1) constituting the ATP-sensitive  $K^+$  channel (hereinafter sometimes abbreviated to  $K_{ATP}$  channel) of pancreatic  $\beta$ -cells to close the  $K_{ATP}$  channel and cause depolarization on the cellular membrane [e.g.  
20 sulfonylurea compound (sulfonylurea antidiabetic agent), fast-acting insulin secretagogue]" has become ineffective in lowering the blood sugar level due to repeated or long-term (e.g. for 2 or more weeks, preferably for 4 or more weeks) administration of said drug.

25 The above-mentioned sulfonylurea compound includes.

compounds having a sulfonylurea skeleton and the derivatives thereof, for example, tolbutamide, glibenclamide, gliclazide, chlorpropamide, tolazamide, acetohexamide, glyclopyramide, glimepiride, glipizide, glybuzole, and the like.

The fast-acting insulin secretagogue includes compounds that promote insulin secretion from pancreatic  $\beta$ -cells as in the case of sulfonylurea compounds, although do not have a sulfonylurea skeleton, for example, glinide compounds such as repaglinide, senaglinide, nateglinide, mitiglinide or its calcium salt hydrate, and the like.

Sulfonylurea secondary failure may be ascribable to either of a sulfonylurea compound and a fast-acting insulin secretagogue.

[0029]

Diabetes of "diabetes with sulfonylurea secondary failure" includes type 1 diabetes, type 2 diabetes, gestational diabetes, impaired glucose tolerance (IGT), impaired fasting glucose (IFG), impaired fasting glycemia (IFG), diabetic complications [e.g. neuropathy, nephropathy, retinopathy, cataract, macroangiopathy, osteopenia, diabetic hyperosmolar coma, infections (e.g., respiratory tract infection, urinary tract infection, alimentary canal infection, dermal soft tissue infection, inferior limb infection, etc.), diabetic gangrene, xerostomia, hypacusis,



cerebrovascular disorder, peripheral blood circulation disorder] and the like. Among these, type 2 diabetes is preferable.

The agent for treating diabetes with sulfonylurea  
5 secondary failure of the present invention shows excellent insulin-secreting and hypoglycemic effects on even diabetic patients on whom a sulfonylurea compound or a fast-acting insulin secretagogue has no insulin-secreting effect and therefore no sufficient hypoglycemic effect.

10 [0030]

A dose of the agent of the present invention varies on a subject to be administered, an administration route, targeted disease and the like. For example, when the agent of the present invention is orally administered to an adult  
15 diabetic patient, the unit dose is usually about 0.01 to 100 mg/kg bodyweight, preferably 0.05 to 30 mg/kg bodyweight, and more preferably 0.1 to 10 mg/kg bodyweight of the active ingredient, a DPP-IV inhibitor. Preferably, the unit dose is administered once or twice a day.

20 [0031]

The agent of the present invention can be used in combination with a drug such as a diabetic treating agent, a diabetic complication treating agent, a hyperlipemia treating agent, a hypotensive drug, an anti-obesity drug, a  
25 diuretic, an antithrombotic drug or the like (hereinafter

abbreviated to a concomitant drug), for the purpose of enhancing the efficacy of or reducing the dose of the agent of the present invention. In this case, the timing for administering the agent of the present invention and a concomitant drug is not restricted. They may be administered simultaneously or separately at an interval of time. Alternatively, the agent of the present invention and a concomitant drug may be administered as two separate preparations containing the respective active ingredients or as a single preparation containing both the active ingredients.

A dose of a concomitant drug can be selected appropriately based on the clinical dose. The combination ratio between the agent of the present invention and a concomitant drug can be selected appropriately depending on a subject to be administered, an administration route, disease to be treated, symptoms and a combination of drugs. In the case where a subject to be administered is a human, 0.01 to 100 parts by weight of a concomitant drug may be used per 1 part by weight of the agent of a DPP-IV inhibitor, the active ingredient of the present invention.

[0032]

The above-mentioned diabetic treating agent includes insulin preparations (e.g., animal-derived insulin preparations extracted from bovine or swine pancreas; human

insulin preparations which are synthesized with genetic engineering using *Escherichia coli* or yeast; insulin zinc; protamine insulin zinc; insulin fragments or derivatives (for example, INS-1) etc.), insulin sensitizers (e.g. pioglitazone or a salt thereof (preferably hydrochloride), 5 rosiglitazone or a salt thereof (preferably maleate), GI-262570, reglixane (JTT-501), netoglitazone (MCC-555), KRP-297, rivoglitazone (CS-011), FK-614, ragaglitazar (NN-622), tesaglitazar (AZ-242), muraglitazar (BMS-298585), EML-16336, 10 compounds described in WO99/58510 (e.g. (E)-4-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyloxyimino]-4-phenylbutyric acid), compounds described in WO01/38325, BM-13-1258, LM-4156, MBX-102, LY-519818, MX-6054, LY-510929, balaglitazone (NN-2344), T-131 or a salt thereof, THR-0921), PPAR $\gamma$  15 agonists, PPAR $\gamma$  antagonists, PPAR $\gamma$ / $\alpha$  dual agonists,  $\alpha$ -glucosidase inhibitors (e.g., voglibose, acarbose, miglitol, emiglitate), biguanide agents [e.g., phenformin, metformin, buformin, or their salts (e.g., hydrochloride, fumarate, succinate)], GLP-1 receptor agonists [e.g. GLP-1, NN-2211, 20 AC-2993 (exendin-4), BIM-51077, Aib(8,35)hGLP-1(7,37)NH<sub>2</sub>], amylin agonists (e.g., pramlintide), phosphotyrosine phosphatase inhibitors (e.g., sodium vanadate),  $\beta$ 3 agonists (e.g. CL-316243, SR-58611-A, UL-TG-307, SB-226552, AJ-9677, BMS-196085, AZ40140), glyconeogenesis inhibitors (e.g., 25 glycogen phosphorylase inhibitors, glucose-6-phosphatase

inhibitors, glucagon antagonists, somatostatin receptor agonists), sodium-glucose cotransporter (SGLT) inhibitors (e.g., T-1095), and the like.

[0033]

5           The diabetic complication treating agent includes aldose reductase inhibitors (e.g., tolrestat, epalrestat, zenarestat, zopolrestat, minalrestat, fidarestat (SNK-860), CT-112), neurotrophic factors and enhancers therefor [e.g., NGF, NT-3, BDNF, neurotrophin production/secretion  
10       promoters described in WO01/14372 (e.g., 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-(3-(2-methylphenoxy)propyl)oxazole) etc.], neural regeneration promoters (e.g. Y-128), PKC inhibitors (e.g., ruboxistaurin mesylate; LY-333531), AGE inhibitors (e.g., ALT946,  
15       pimagedine, piratoxathin, N-phenacylthiazolium bromide (ALT766), EXO-226), reactive oxygen scavengers (e.g., thioctic acid), cerebral vasodilators (e.g., tiapride, mexiletine).

          The hyperlipemia treating agent includes statin  
20       compounds that acts as cholesterol synthesis inhibitors (e.g., cerivastatin, pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin, pitavastatin, rosuvastatin or their salts (sodium salts, calcium salts)), squalene synthase inhibitors (e.g., compounds described in  
25       WO97/10224, for example, N-[[ (3R,5S)-1-(3-acetoxy-2,2-

dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-  
 1,2,3,5-tetrahydro-4,1-benzoxazepine-3-  
 yl]acetyl]piperidine-4-acetic acid, etc.), fibrate  
 compounds (e.g., benzafibrate, clofibrate, simfibrate,  
 5 clinofibrate), ACAT inhibitors (e.g., avasimibe,  
 eflucimibe), anion-exchange resins (e.g., cholestyramine),  
 probucol, nicotinic acid drugs (e.g., nicomol, niceritrol),  
 ethyl icosapentate, phytosterol (e.g., soysterol,  $\gamma$ -  
 oryzanol), and the like.

10       The hypotensive drug includes angiotensin converting  
 enzyme inhibitors (e.g., captopril, enalapril, delapril),  
 angiotensin II antagonists (e.g., candesartan, cilexetil,  
 losartan, eprosartan, valsartan, telmisartan, irbesartan,  
 tasosartan, olmesartan medoxomil, 1-[[2'-(2,5-dihydro-5-  
 15 oxo-4H-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]-2-ethoxy-  
 1H-benzimidazole-7-carboxylic acid), calcium antagonists  
 (e.g., manidipine, nifedipine, amlodipine, efonidipine,  
 nicardipine), potassium channel openers (e.g.,  
 levcromakalim, L-27152, AL 0671, NIP-121), clonidine, and  
 20 the like.

      The anti-obesity drug includes anti-obesity drugs  
 acting on the central nervous system [e.g., dexfenfluramine,  
 fenfluramine, phentermine, sibutramine, amphepramone,  
 dexanphetamine, mazindol, phenylpropanolamine, clobenzorex],  
 25 pancreatic lipase inhibitors (e.g., orlistat, ATL-962),  $\beta$ 3

agonists (e.g., CL-316243, SR-58611-A, UL-TG-307, SB-226552, AJ-9677, BMS-196085, AZ-40140), peptidic anorectics (e.g., leptin, CNTF (ciliary neurotrophic factors)), cholecystokinin agonists (e.g., lintitript, FPL-15849), and the like.

[0034]

The diuretic includes xanthine derivatives (e.g., sodium salicylate theobromine, calcium salicylate theobromine), thiazide agents (e.g., ethiazide, cyclopenthiazide, trichlormethiazide, hydrochlorothiazide, hydroflumethiazide, benzylhydrochlorothiazide, penflutizide, polythiazide, methyclothiazide), anti-aldosterone drugs (e.g., spironolactone, triamterene), carbonic anhydrase inhibitors (e.g., acetazolamide), chlorobenzenesulfonamide drugs (e.g., chlorthalidone, mefruside, indapamide), azosemide, isosorbide, etacrynic acid, piretanide, bumetanide, furosemide, and the like.

[0035]

The antithrombotic drug includes heparin (e.g., heparin sodium, heparin calcium, dalteparin sodium), warfarin (e.g., warfarin potassium), anti-thrombin agents (e.g., aragatroban), thrombolytic agents (e.g., urokinase, tisokinase, alteplase, nateplase, monteplase, pamiteplase), platelet aggregation inhibitors (e.g., ticlopidine hydrochloride, cilostazol, ethyl icosapentate, beraprost

sodium, sarpogrelate hydrochloride), and the like.

Preferred concomitant drug is an insulin preparation, an insulin sensitizer, an  $\alpha$ -glucosidase inhibitor, a biguanide or the like.

5 [0036]

The present invention further relates to "an insulin secretagogue for diabetic patients with sulfonylurea secondary failure which comprises a DPP-IV inhibitor".

10 The DPP-IV inhibitor and the diabetes with sulfonylurea secondary failure are as defined above.

The above-mentioned insulin secretagogue can be produced using a DPP-IV inhibitor and then used, similarly to the above-mentioned agent for treating diabetes with sulfonylurea secondary failure. The insulin secretagogue is useful as an agent for treating diabetes with sulfonylurea secondary failure, and shows excellent insulin-secreting and hypoglycemic effects on even diabetic patients on whom a sulfonylurea compound or a fast-acting insulin secretagogue has no insulin-secreting effect and therefore no sufficient hypoglycemic effect.

15  
20

The present invention further relates to "a closer of the ATP-sensitive  $K^+$  channel that has become unable to be closed as a result of stimulation by a sulfonylurea receptor 1-binding compound (e.g. sulfonylurea compound, fast-acting insulin secretagogue) comprising a DPP-IV

25

inhibitor".

The DPP-IV inhibitor, the sulfonylurea compound and the fast-acting insulin secretagogue are as defined above.

The above-mentioned closer can be produced using a DPP-IV inhibitor and then used, similarly to the above-mentioned agent for treating diabetes with sulfonylurea secondary failure. The closer is specifically useful as an agent for treating diabetes with sulfonylurea secondary failure.

10 [0037]

The present invention is illustrated in further detail by the following Example and Experimental Example which are not intended to limit the present invention and may vary within the scope of the present invention.

15 In the following Example and Experimental Example, 2-{{[3-(aminomethyl)-2-isobutyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolinyloxy}acetamide monohydrate is abbreviated to Compound A.

[0038]

20 Example 1

Compound A (150 mg), lactose (1184 mg), corn starch (360 mg), HPC-L (trade name, manufactured by Nippon Soda Co., Ltd.) (60 mg), carboxymethylcellulose calcium (trade name: ECG505, manufactured by Gotoku Chemical Company Ltd.) (60 mg), crystalline cellulose (trade name: Avicel,



manufactured by Asahi Kasei Corporation) (172 mg), and magnesium stearate (14 mg) were mixed in a mortar. 200 mg of the resultant mixture was compressed using a hydraulic pump press (manufactured by Riken Seiki Co., Ltd.) to  
5 obtain a tablet with a diameter of 8 mm.

[0039]

#### Experimental Example 1

##### Preparation of N-STZ-1.5 rat

Streptozocin (STZ) (120 mg/kg bodyweight) was  
10 administered to a 1.5-day-old male WKY rat to obtain a type 2 diabetes model, N-STZ-1.5 rat.

N-STZ-1.5 rats (male, 24 animals) received orally glibenclamide (10 mg/kg bodyweight/day) for 4 weeks to become a model of type 2 diabetes with sulfonylurea  
15 secondary failure. Then, the rats were divided into 4 groups of Groups A to D (6 animals each). Group A (control group), Group B, Group C and Group D were treated with oral administration of a 0.5% methylcellulose suspension,  
20 glibenclamide (10 mg/kg bodyweight), nateglinide (50 mg/kg bodyweight) and Compound A (3 mg/kg bodyweight), respectively. (Hereinafter, the methylcellulose suspension, glibenclamide, nateglinide and Compound A administered to Groups A to D are sometimes collectively referred to as the test compound.)

25 Then, each rat received orally 1 g/kg bodyweight of

glucose solution. Before administration of glucose (before and after administration of the test compound) and 10 and 60 minutes after administration of glucose solution, blood samples were taken from the caudal vein of the rat and then the plasma glucose level and the plasma insulin level were determined.

The plasma glucose level was determined by an enzymatic method using L type WakoGlu2 (trade name, Wako Pure Chemical Industries, Ltd.), and the plasma insulin level was determined by radioimmunoassay using Shionoria Insulin Kit (trade name, Shionogi & Co., Ltd.).

The increment of plasma glucose level 60 minutes after administration of glucose solution (from 0 to 60 minutes after sugar loading); the increment of plasma insulin level 10 minutes after administration of glucose solution (from before administration of the test compound to 10 minutes after sugar loading); and the increment of plasma insulin level 10 minutes after administration of glucose solution (from 0 to 60 minutes after sugar loading) are shown in Table 1, Table 2 and Table 3, respectively. The values in the tables are mean values (n=6).

Table 1

Group	Increment of plasma glucose level (mg/dl)
Group A (control)	172.72
Group B (glibenclamide)	180.65
Group C (nateglinide)	185.95
Group D (Compound A)	134.83

Table 2

Group	Increment of plasma insulin level ( $\mu$ U/ml)
Group A (control)	19.37
Group B (glibenclamide)	18.03
Group C (nateglinide)	18.76
Group D (Compound A)	44.06

5           As seen in Table 1, administration of glibenclamide  
 (sulfonylurea compound) or nateglinide (fast-acting insulin  
 secretagogue) to the type 2 diabetic rat with sulfonylurea  
 secondary failure had no plasma glucose level-lowering  
 effect, but administration of Compound A (DPP-IV inhibitor)  
 10       achieved excellent plasma glucose level-lowering effect.

          As seen in Table 2 and Table 3, administration of  
 glibenclamide (sulfonylurea compound) or nateglinide (fast-  
 acting insulin secretagogue) to the type 2 diabetic rat  
 with sulfonylurea secondary failure had hardly plasma  
 15       insulin level-elevating effect, but administration of  
 Compound A (DPP-IV inhibitor) achieved excellent plasma  
 insulin level-elevating effect.

Industrial Applicability

[0040]

The agent for treating diabetes with sulfonylurea  
secondary failure of the present invention shows excellent  
insulin-secreting and hypoglycemic effects on even diabetic  
5 patients on whom a sulfonylurea compound or a fast-acting  
insulin secretagogue has no insulin-secreting effect and  
therefore no sufficient hypoglycemic effect

Document Name: Abstract

Problem: To provide an agent for treating diabetes with  
sulfonylurea secondary failure showing excellent insulin-  
secreting and hypoglycemic effects on even diabetic

5 patients on whom a sulfonylurea compound or a fast-acting  
insulin secretagogue has no insulin-secreting effect and  
therefore no sufficient hypoglycemic effect.

Solution: An agent for treating diabetes with sulfonylurea  
secondary failure which comprises a dipeptidyl peptidase IV  
10 inhibitor.

Selected Figure: none